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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/416,384	10/12/1999	MARTA BLUMENFELD	GENSET.045AU	6101

7590 09/20/2002

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	29

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/416,384	Blumenfeld et al
Examiner	**Art Unit**
Jeffrey Fredman	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Sep 11, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *three* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
see attached sheet.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: *58, 62, and 73-75*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ .

10. ☐ Other:

JEFFREY FREDMAN
PRIMARY EXAMINER
ART UNIT 1637

Response to Arguments

1. Applicant's arguments filed September 11, 2002, have been fully considered but they are not persuasive.

Applicant reiterates the arguments previously made.

Applicant argues that the current application has substantial and specific utility. Applicant argues that the issue for substantial utility is whether it is more likely than not that proteins containing polyglutamine repeats are associated with neurodegenerative diseases. Applicant argues that it is more likely than not based upon the expression of the G713 protein in the brain, the association of 12 diseases with CAG repeat containing proteins.

However, these arguments fail to address the central question implicated in the analysis of substantial utility. As the Utility guidelines note, "Utilities that require or constitute carrying out further research to identify or reasonably confirm a "Real world" context of use are not substantial utilities (page 6 of guidelines)". The current case represents a situation where the protein lacks any known substantial utility. Contrary to applicant's arguments, the protein is NOT shown to be associated with any neurodegenerative disease, the protein is ONLY a candidate gene for such an association. The association of the genomic region is not significant because it does not associate this protein with schizophrenia, since many genes may be within the region. The argument that the protein is expressed in brain is not persuasive given that Applicant states

that thousands of proteins are expressed in brain, many of which have no particular phenotype associated with them.

Applicant argues that the use of three glutamine repeats in screening the genomic database is not a fair comparison because G713 has more than 3 repeat sequences. Applicant is relying, in argument, upon the association of glutamine repeat sequences with neurological disease. Therefore, it is perfectly fair to ask whether glutamine repeat sequences alone are limited to such an association. As the finding of 6,723 human sequences with 3 CAG repeating units shows, no such association can be made for all glutamine repeats. As a follow up, however, for 4 CAG repeating units, a search in STN finds 3,882 such human sequences. For 5 CAG repeating units, a search in STN finds 1,773 such human sequences. For 6 CAG repeating units, a search in STN finds 1,068 such human sequences. For 7 CAG repeating units, a search in STN finds 646 such human sequences. Even for 9 CAG repeating units, a search in STN still finds 310 such human sequences. Thus, even 9 CAG repeating units are found in a large number of human sequences, including 249 different publications, no assoication is found solely with neurological disease and glutamine repeating sequences.

This situation tracks example 5 of the Utility guidelines, where a protein is characterized, and in that example, some function was found for the protein unlike here. However, that function was found insufficient because further experimentation was necessary to attribute a use to the protein. The Supreme Court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an

immediately apparent or fully disclosed "real world" utility. The Court in Brenner v. Manson, 383 U.S. 519 (1966) held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a protein of as yet undetermined function or biological significance.

With regard to substantial utility, there must be some correlation or relationship between the claimed protein and a disease or disorder. The presence of a protein in tissue that is derived from disease cells is not sufficient for establishing a substantial utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed protein to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed protein is either present only in disease tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed protein as a diagnostic for a disease. However, in the absence of any disclosed relationship between the

claimed protein or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed protein or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

With regard to specific utility, Applicant traverses the cited Perutz and Kashima papers. Applicant argues that Perutz teaches some neurodegenerative diseases associated with glutamine repeats. This does not detract from the central point supported by Perutz, which is that glutamine repeats alone are not specific to neurodegenerative diseases. Other diseases such as muscular dystrophy are also associated with glutamine repeats, so that no specific utility can be based solely upon the presence of absence of such repeats.

Applicant's arguments against the Kashima's reference disclosure that a protein, not expressed in brain, but containing glutamine repeats, is irrelevant, misses the force and point being made in citation of Kashima. Kashima shows that no specific association of neurodegenerative disease and glutamine repeats is necessary. Kashima shows that entirely unrelated proteins may have glutamine repeats but be have no specific association with neurodegenerative diseases. Given that no evidence of a specific association with any specific disease is provided in the specification for the claimed G713 protein, Kashima underlies a central point. Kashima found that

glutamine repeats had no specific utility in the activity of MIL-2. Given the absence of any evidence, it is solely the object of further research to determine whether glutamine repeats play any role in the activity of G713, if that protein even has any activity whatsoever.

Applicant then argues the 112, first paragraph enablement rejection. Most of the arguments are identical to those already addressed. However, Applicant challenges the Wright papers showing of unpredictability in linkage of schizophrenia by citing Weinberger. The fact that there is significant debate over whether any particular chromosomal locations are actually linked to schizophrenia supports the unpredictability and does not undermine it. Weinberger does not identify any specific loci associated with schizophrenia but simply identifies a brain region associated with the disease, an entirely unrelated and irrelevant approach with regard to this application.

Therefore, given that the unpredictability of the linkage remains, the conclusion of undue experimentation will not be disturbed.